Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak.

Running tittle: smell recovery in COVID-19.

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Abstract:

Background: Post-viral olfactory dysfunction is well established and has been shown to be a key symptom of the Coronavirus diseases 2019 with more than 66% European and U.S patients reporting some degree of loss of smell. Persistent olfactory dysfunction appears to be commonplace and will drive the demand for General Practitioner, Otolaryngology or Neurology consultation in the next months - evidence regarding recovery will be essential in counselling our patients.

Methods: prospective survey-based data collection and telemedicine follow-up.

Results: 751 patients completed the study. The mean age of patients was 41 ± 13 (range: 18 – 60). There were 477 females and 274 males. There were 621 patients (83%) who subjectively report a total loss of smell and 130 (17%) a partial loss. After a mean follow-up of 47±7 days (range: 30–71) from the first consultation, 277 (37%) of patients still reported a persistent subjective loss of smell, 107 (14%) reported partial recovery and 367 (49%) reported complete recovery. The mean duration of the OD was 10±6 days (range: 3–31) in those patients who completely recovered and 12±8 days (range: 7–35) in those patients who partially recovered.

Conclusions: According to our results, at this relatively early point in the pandemic, subjective patterns of recovery of olfactory disfunction in COVID-19 patients are valuable for our patients, hypothesis generation and treatment development.

Key words: COVID-19; anosmia; olfaction; smell; recovery; coronavirus.

Introduction:

As of 10th May 2020, nearly 4 million global citizens across 215 countries have tested positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] Post-viral olfactory dysfunction (OD) is well established,[2] and has been shown to be a key symptom of the Coronavirus diseases 2019 (COVID-19), with more than 66% European and U.S patients reporting some degree of loss of smell.[3-5] We have apparently overcome the worst part of the initial outbreak. However, persistent OD appears to be commonplace and will drive the demand for General Practitioner, Otolaryngology or Neurology consultation in the next months - evidence regarding recovery will be essential in counselling our patients.

Method:

In order to evaluate patterns of olfactory recovery, data from patients with confirmed COVID-19 were collected prospectively from 3 University Hospitals. Adults (>18yo) with a positive test for SARS-CoV-2 via reverse transcription polymerase chain reaction (RT-PCR) or a positive IgG/IgM were included. Those with symptom duration <14 days were tested with a nasopharyngeal swab; in the case of negative RT-PCR or patients with symptoms for ≥14 days, serology testing was performed. Only patients with a positive RT-PCR or with positive IgG/IgM were included (Figure 1). All patients had at least 30-days of follow-up after their last negative subsequent COVID-19 test. (Figure 1)

Patients with pre-existing olfactory or gustatory dysfunction; without a laboratory-confirmed COVID-19 infection diagnosis and those requiring intensive-care at the time of the study were excluded. Information was collected using an online questionnaire created with Professional Survey Monkey (San Mateo, California, USA). Informed consent was obtained.

Relevant epidemiological and clinical features contained within the questionnaire were collected by the COVID-19 Study Group of Young Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies (YO-IFOS), and consisted of 4 subsets (Demographic data, medical background, ENT symptoms and Olfactory and Gustatory disfunction). All patients completed the Short version of Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS).[6] The remaining olfactory and taste questions were based on the smell and taste component of the National Health and Nutrition Examination Survey.[7] Physical examination (rhinoscopy, nasal endoscopy or objective olfactory testing) was not performed in this study due to the risk of nosocomial infection.

Statistical Package for the Social Sciences for Windows (SPSS version 21,0; IBM Corp, Armonk, NY, USA) was used to perform the statistical analyses. The potential associations between epidemiological, clinical and olfactory and gustatory outcomes have been assessed through cross-tab generation between two variables (binary or categorical variables) and Chi-square test. Incomplete responses were excluded from analysis. The differences in sQOD-NS scores between patients regarding the olfactory dysfunction during the first evaluation and after almost 30 days of follow-up were made through the Kruskal–Wallis test. A level of $p < 0.05$ was used to determine statistical significance. A multivariate analysis was performed to address possible confounders.

Results:

All told, 1411 patients identified in the emergency room or primary care consultation were invited to participate in the study. A total of 1231 patients agreed to participate, and 751 patients completed the study (Supplementary material). The mean age of patients was 41 ± 13 (range: 18 – 60). There were 477 females and 274 males. The groups were comparable according to age, sex ratio, comorbidities and addiction (p=0.273, Wilcoxon). There were 621 patients (83%) who subjectively report a total loss of smell and 130 (17%) a partial loss. After a mean follow-up of 47±7 days (range: 30–71) from the first consultation, 277 (37%) of patients still reported a persistent subjective loss of smell, 107 (14%) reported partial recovery and 367 (49%) reported complete recovery. The mean duration of the OD was 10±6 days (range: 3–31) in those patients who completely recovered and 12±8 days (range: 7–35) in those patients who partially recovered (Table 1 and figure 1).

Treatments used during the follow-up period varied, with 71 patients (9%) using nasal corticosteroid spray, 58 (8%) using oral steroid and 149 (20%) using nasal saline irrigation. There was no significant correlation between the use of nasal spray (p=0.324), oral steroid (p=0.211) or nasal irrigation (p=0.453) and olfactory recovery. We found significant difference in initial nasal symptoms or sQOD-NS score with recovery being significantly lower in patients with a total loss of smell

compared with those patients with a partial loss of smell or normosmic during the first consultation and after almost 30-days of follow-up (p=0.001). There was no significant association between comorbidities and the development or persistence of OD (Table 2).

Discussion:

Hopkins *et al*. recently found that nearly 80% of patients experienced improvement in loss of smell within a few weeks of onset, with recovery rates appearing to plateau after 3 weeks.[8] We found that nearly 63% of patients report improvement in their subjective loss of sense of smell after at least 4 weeks. However, the frequency of residual OD after 30 days of follow-up was significant and despite the possibility of a later recovery, it is necessary to highlight that the higher incidence of COVID-19 patients affected allow us to infer that a large amount of patients will suffer from a long-term OD.

Currently the mechanism for anosmia is not clear, some evidence suggests viral spread through the neuroepithelium of the olfactory cleft, with the consequent infiltration of the olfactory bulb and the central nervous system as the main cause. This theory is supported by the increasing evidence about nasal respiratory epithelial cells and olfactory epithelial support cells who may express moderate-to-high levels of angiotensin converting enzyme-2 (ACE2) proteins used as a carrier by the SARS-CoV-2 to infect cells.[9] However, more evidence is necessary to elucidate the real mechanism for the OD.

Limitations of this study are the exclusion of patients with severe disease, the small proportion of older patients, the higher proportion of female respondents, loss to follow-up and recruitment from ENT-Clinics, potentially introducing a selection bias. Lack of objective testing to confirm anosmia is also a limitation. However, at this relatively early point in the pandemic, subjective patterns of recovery of OD in COVID-19 patients are valuable for our patients, hypothesis generation and treatment development.

Authorship:

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Ethics approval and consent to participate:

Four ethics committees approved the current study protocol (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303; CHU-Charleroi:B32522020).

Availability of data and materials

Data may be available upon a reasonable request and an approval from the originating university hospitals.

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Figure 1:

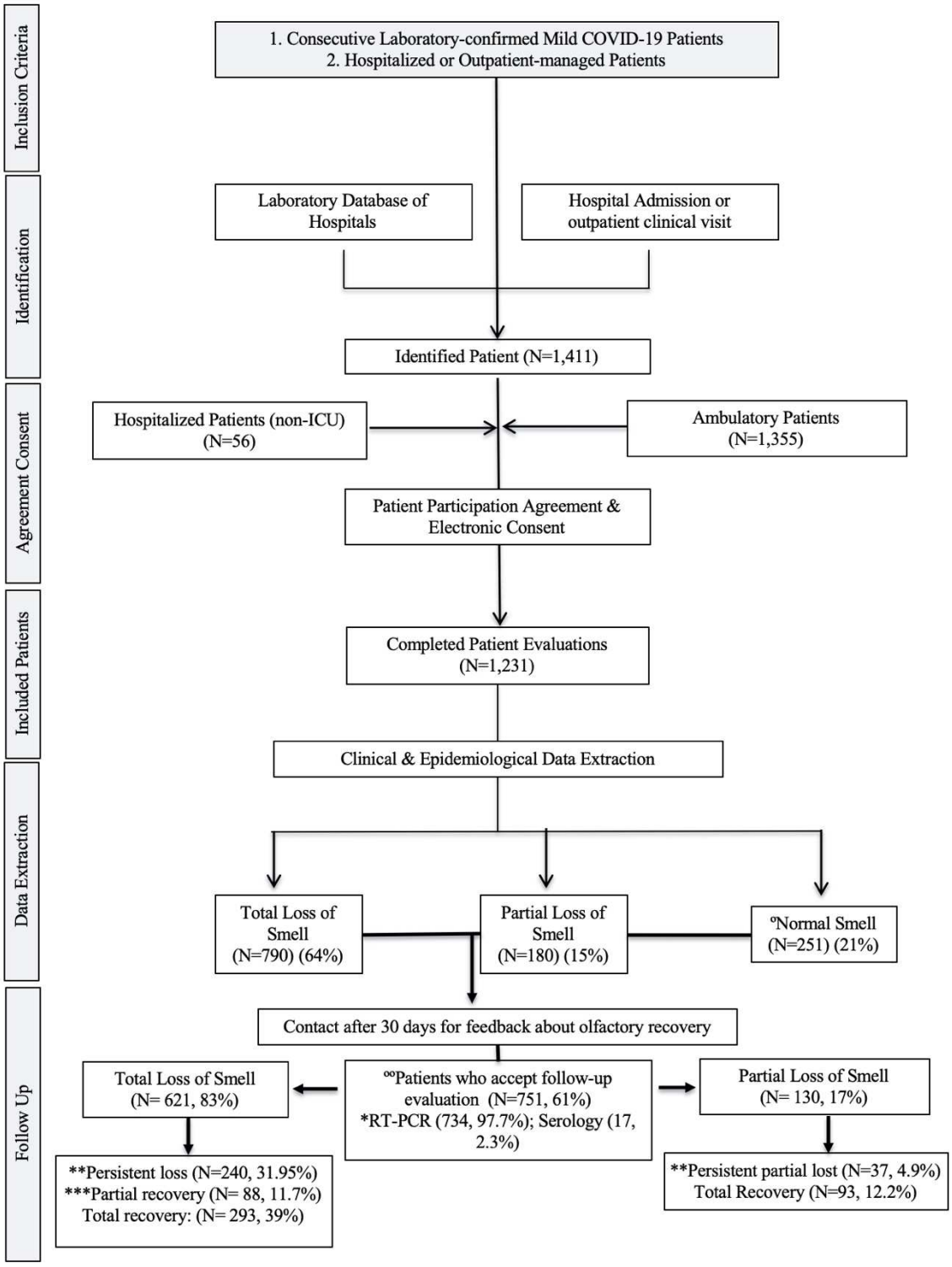

Figure 1. Study Flowchart. ºEleven patients initially considered in the group of normal smell develop an olfactory disfunction. ººFour-Hundred and eighty patients were not included due to the incomplete follow-up data (362, 75,4%), lost in follow-up by impossibility to contact the patient (61, 12,7%), because they refused to participate for personal reasons (48, 10%) or due to need for ICU Admission (9, 1.9%). *To consider COVID-19 negative patients were tested almost three times.**

Persistent lost were considered in those patient who do not report any improvement.***Partial recovery were considered in those patient who subjectively start to smell some odors.